Citation:

Gochfeld M, Burger J. Good fish/bad fish: a composite benefit-risk by dose curve. *Neurotoxicology*. 2005 Aug;26(4):511-20.

PubMed ID: 15979722

Study Design:

Meta-analysis

Class:

M - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine dose-response information for the benefits and harm of fish consumption, and to present a composite dose-response curve (for methylmercury) which elucidates the benefit-harm paradox, identifies data needs (thresholds and asymptotes), and informs personal decisions about which and how much fish to consume as well as enhancing the fish advisory process.

Inclusion Criteria:

- Studies presented data on fish consumption either in meals per month or grams per day (g/day) in relation to adult cardiovascular risks
- Studies provided data on threshold and asymptote for methylmercury in fish
- For the benefits analysis, only papers that provided data on fish consumption (vs fish oil supplements) were included

Exclusion Criteria:

- None specified

Description of Study Protocol:

Literature Search:

- MEDLINE searched, using various combinations of terms, for literature on
  - risks from methylmercury and polychlorinated biphenyls in fish
  - benefits of fish consumption
  - studies of polyunsaturated fatty acids (PUFA)
  - studies of fish oil consumption

Design: Meta-analysis

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

- Logistic dose-response curve drawn for benefits, aligned with estimate of threshold and asymptote
- To estimate harm threshold:
  - lowest allowable daily intake recognized by national or international agencies used: 0.1 ug/kg/day (U.S.A. Environmental Protection Agency Reference Dose, RfD)
  - less strict value also used: 0.3 ug/kg/day minimum risk level (MRL) proposed by the Agency for Toxic Substances and Disease Registry

Data Collection Summary:

Timing of Measurements: not applicable

Dependent Variables

- Developmental and adult cardiovascular benefits of fish consumption

Independent Variables

- Fish consumption: usually by dietary recall in studies: 1 meal assumed to = 8 oz. fish (227 g)
- To estimate toxicity from methylmercury concentration of fish: 9 types of fish most commonly available in New Jersey markets (not including canned tuna)

Control Variables

Description of Actual Data Sample:

Initial N: 13 cohort studies on adult cardiovascular risks and fish consumption identified

Attrition (final N): 7 studies yielded threshold data and asymptote, plus review of one published meta-analysis

Age: not applicable

Ethnicity: not applicable

Other relevant demographics

Anthropometrics

Location: New Jersey markets

Summary of Results:

Key Findings

- Analysis of the 9 most common fish in New Jersey markets yielded a weighted average methylmercury concentration of 0.23 ug/g (ppm wet weight).
- There are great disparities in the amount and distribution of both PUFAs and contaminants in different fish species
- The duration of pregnancy and birth weight improve at a benefit threshold of about 8 - 15 g/day maternal fish intake
- Meta-analyses reveal adult cardiovascular benefits around 7.5 - 22.5 g/day bracket, yielding a midpoint also at 15 g per day
- Benefit asymptotes are above 45 g/day and in some studies exceed 100 g/day
- Using the EPA reference dose of 0.1 ug/kg as a methylmercury threshold, the fish intake threshold for harm converts to 27 g/day (for a selection of common commercial fish averaging 0.23 ppm MeHg) to 65 g/day for someone choosing fish low in MeHg (0.1 ppm).
- People who ate fish at least 1/month had lower RR (not always statistically significant at P=0.05) than those who ate fish less frequently or not at all
    - benefits for both heart disease and stroke begin in the 15 - 35 g/day range
    - reproductive benefits appear to have a threshold in the same range, based on very limited data
    - asymptotes are harder to detect
        - some studies show little benefit to increasing above 45 g/day
        - other studies show benefit in the highest consumption group
            - risks from contaminants may erase benefits

Fish Consumption: Dose and Toxicity

- The benefit threshold for several endpoints (pregnancy duration and development, and adult cardiovascular) consistently lie below the thresholds for harm from methylmercury
- Sample of 9 types of fish most commonly available in New Jersey:
    - weighted mean total mercury level of 0.26 ug/g (ppm wet weight), corresponding to about 23 ug/g of methylmercury
        - thus, women who consume a variety of fish, could eat 26.5 g/day, or 80 g/day (3 to 9 eight ounce meals/month) before exceeding the RfD and MRL, respectively
- Composite Benefit-Risk by Dose Curve suggests:
    - 15 g/day appears to be a common benefit threshold from several studies and endpoints
    - developmental benefits may occur as low as 5 g/day
    - 27 g/day corresponds to the worst case harm threshold for a person consuming fish averaging 0.23 ug/g of methylmercury
    - 60 g/day corresponds to a harm threshold for a person selecting fish known to be low in methylmercury (0.10 ug/g)
    - 45 g/day corresponds to the lowest asymptote for benefits from fish consumption

Fish Consumption: Dose and Benefits

- Developmental (i.e reproductive) benefits
    - prospective study of pre-term births (N=8998 women)
        - women who consumed no fish were 3.6 times more likely (95% CI: 1.15 - 11.2x) to have a pre-term birth than women who consumed 38 g fish per day
- Cardiovascular benefits (see table)
- CHD
    - Western Electric Company Study:
        - men who ate any fish had slightly reduced deaths from coronary heart disease (CHD) and myocardial infarction (MI)

- more obvious benefit above ~ 26 g/day (interpolated between 18 and 34 g/day)
- Above 35 g fish/day, relative risks (RR) compared with no fish intake:
  - fatal CHD = 0.62
  - fatal MI = 0.56
  - non-sudden death from heart disease = 0.33
- no clear maximum benefit shown

- Harvard Health Professionals study (1995)
  - there was an unexpected increased likelihood of heart surgery in the high PUFA intake group
  - there was a protective effect against MI and CHD
    - threshold: 14 - 28 g/day range
    - asymptote: ~ 80 g/day
- study in Italian women (1990)
  - similar results to Harvard Health Professionals study
    - threshold for non-fatal MI: 32 g/day
    - asymptote: > 64 g/day
- data on American men and women (2000)
    - threshold for cardiac arrest: ~ 15 g/day
    - continued benefit among frequent fish eaters
- study of physicians (1998)
  - RR for sudden death for those who ate 1 fish meal per week (32 g/day) = 0.44
    - threshold around 14g/day
    - asymptote: > 45 g/day
- Zutphen study (1985)
  - men who reported eating fish had a lower rate of CHD death
    - threshold: 30g/day
  - data are compatible with RR of 0.60 for 14g/day
    - benefit plateau after 44g/day
- Meta-analysis (2004) (review of 11 papers including most in this review)
  - significant risk reduction even at 7.5 - 22.5 g/day (1-3 meals/month) compared with the less than 1 meal/month category
  - there appeared to be a plateau at about 1 meal/week followed by even further improvement at >4 meals/week

- Stroke
  - one study (1994) found a protective effect against stroke with a threshold possibly as low as 8 g/day
  - however, greater stroke risk was found with increasing fish consumption (2002)
  - U.S. physicians (2004)
    - stroke-protective benefit at 1-3 meals/month (midpoint = 15 g/day)
    - no added benefit from greater fish consumption
    - main protection was against ischemic strokes
    - protection against hemorrhagic stroke only in most frequent fish eater groups
  - Nurses Health study
    - women who ate fish 1-3 times/month: RR = 0.79
    - women who ate fish weekly: RR = 0.71
    - little added benefit from more frequent consumption
    - threshold for benefit: 15 g/day (1-3 meals/month) (midpoint)
    - benefit plateau: ~45 g/day
    - threshold for protection against stroke also seen at 30 g/day, mainly for

thrombotic rather than hemorrhagic stroke

Author Conclusion:

There are benefits to eating fish, and to some extent these benefits derive from their PUFA content. Choosing fish low in methylmercury and polychlorinated biphenyls and high in PUFA is clearly desirable, although many people who like fish show a preference for the taste of predatory species, high in methylmercury and not necessarily high in PUFAs. Ongoing research should clarify the dose-benefit and dose-harm curves.

Reviewer Comments:

Research Design and Implementation Criteria Checklist: Review Articles

Relevance Questions		
1.	Will the answer if true, have a direct bearing on the health of patients?	Yes
2.	Is the outcome or topic something that patients/clients/population groups would care about?	Yes
3.	Is the problem addressed in the review one that is relevant to nutrition or dietetics practice?	Yes
4.	Will the information, if true, require a change in practice?	N/A

Validity Questions		
1.	Was the question for the review clearly focused and appropriate?	Yes
2.	Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search termsused described?	Yes
3.	Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	Yes
4.	Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	Yes
5.	Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	Yes
6.	Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	Yes
7.	Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described?	Yes

8.	Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Yes
9.	Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Yes
10.	Was bias due to the review's funding or sponsorship unlikely?	Yes